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Association Between Statin Medications and Mortality, Major Adverse Cardiovascular Event, and Amputation-Free Survival in Patients With Critical Limb Ischemia

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Objectives The aim of this study was to determine the associations between statin use and major adverse cardiovascular and cerebrovascular events (MACCE) and amputation-free survival in critical limb ischemia (CLI) patients.

Background CLI is an advanced form of peripheral arterial disease associated with nonhealing arterial ulcers and high rates of MACCE and major amputation. Although statin medications are recommended for secondary prevention in peripheral arterial disease, their effectiveness in CLI is uncertain.

Methods We reviewed 380 CLI patients who underwent diagnostic angiography or therapeutic endovascular intervention from 2006 through 2012. Propensity scores and inverse probability of treatment weighting were used to adjust for baseline differences between patients taking and not taking statins.

Results Statins were prescribed for 246 (65%) patients. The mean serum low-density lipoprotein (LDL) level was lower in patients prescribed statins (75 ± 28 mg/dl vs. 96 ± 40 mg/dl, $p < 0.001$). Patients prescribed statins had more baseline comorbidities including diabetes, coronary artery disease, and hypertension, as well as more extensive lower extremity disease (all p values <0.05). After propensity weighting, statin therapy was associated with lower 1-year rates of MACCE (stroke, myocardial infarction, or death; hazard ratio [HR]: 0.53; 95% confidence interval [CI]: 0.28 to 0.99), mortality (HR: 0.49, 95% CI: 0.24 to 0.97), and major amputation or death (HR: 0.53, 95% CI: 0.35 to 0.98). Statin use was also associated with improved lesion patency among patients undergoing infrapopliteal angioplasty. Patients with LDL levels >130 mg/dl had increased HRs of MACCE and mortality compared with patients with lower levels of LDL.

Conclusions Statins are associated with lower rates of mortality and MACCE and increased amputation-free survival in CLI patients. (J Am Coll Cardiol 2014;63:682–90) © 2014 by the American College of Cardiology Foundation

Peripheral arterial disease (PAD) affects 4 to 8 million people in the United States (1–3). Patients with PAD have significantly increased rates of myocardial infarction (MI), cardiovascular mortality, and stroke (4). Critical limb ischemia (CLI), the most advanced form of PAD, is characterized by ischemic rest pain, nonhealing ischemic ulcers, and gangrene. Patients with CLI have a major amputation rate as high as 40% at 6 months and a mortality rate of 20% to 25% in the first year after presentation (5,6). Although CLI represents only a subset of the total PAD population, the high cardiovascular event and amputation rates in these patients result in a large overall healthcare burden (7,8).

See page 691

The benefits of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) for morbidity and mortality have been established in patients with or at high risk of ischemic heart disease (9–12). There is also evidence of the

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utility of statins in patients with PAD; a revision of the Adult Treatment Panel III (ATP III) guidelines designates PAD a "coronary heart disease risk equivalent," and consensus guidelines recommend statin therapy to target a low-density lipoprotein (LDL) level of ≤100 mg/dl (2.59 mmol/l) for "very high risk" patients (4,13). However, these recommendations are based predominantly on data from patients with claudication or population screening ankle-brachial indexes (ABIs). Thus, the value of statin therapy for patients with CLI is uncertain.

We hypothesized that statin therapy would be associated with a reduced rate of major adverse cardiovascular and cerebrovascular events (MACCE) and a reduced rate of major amputation in patients with CLI. We tested this hypothesis in a large cohort of patients with CLI who were treated longitudinally at a multidisciplinary vascular center.

Abbreviations and Acronyms

ABI = ankle-brachial index
ATP III = Adult Treatment Panel III
CAD = coronary artery disease
CI = confidence interval
CLI = critical limb ischemia
HR = hazard ratio
LDL = low-density lipoprotein
MACCE = major adverse cardiovascular and cerebrovascular event(s)
MI = myocardial infarction
PAD = peripheral arterial disease

Methods

Design. The PAD-UCD Registry comprises all patients with a clinical diagnosis of PAD who underwent diagnostic angiography and/or therapeutic endovascular intervention at the UC Davis Medical Center from 2006 to 2012. During this interval, 3 vascular surgeons and 1 interventional cardiologist performed all of the procedures. At the time of data analysis, the registry included 975 patients and 1,490 procedures. The study protocol was approved by the Institutional Review Board at the University of California, Davis Medical Center.

Data collection and definitions. We identified patients who had at least 1 presentation during the study period for CLI, defined as Rutherford class 4 to 6 disease (rest pain, nonhealing ulceration due to arterial insufficiency, or gangrene) (14). We retrospectively analyzed these patients' data on the basis of a review of electronic medical record documentation. We used pre- and post-procedure hospital and clinic records to identify patient demographics, baseline health status and medical management, clinical presentation, vascular procedures, post-procedure management, and outcomes. All records were reviewed by trained chart abstractors and verified by a board-certified cardiologist. Patients were categorized into the statin group if either their hospitalization data or the most recent pre-procedure clinic visit indicated current statin use. Other medication prescriptions were determined based on the most recent pre-procedure clinic visit. Baseline serum LDL levels were determined using the most recent value within 6 months pre-procedure.

Routine practice at our institution during this period was to schedule follow-up visits within 1 month after angiographic procedures, then every 3 months for the first year and every 6 to 12 months thereafter. At these visits, patients were assessed for clinical improvement, and those who had interventions were evaluated with interval ABI measurements and duplex ultrasonography.

Outcomes. The primary endpoint was a composite measure of MACCE, defined as any death, MI, or stroke within 1 year post-procedure. MI was defined as symptoms of chest pressure and elevation of troponin with evidence of infarct by stress imaging or coronary angiography and ventriculography. Stroke was defined as focal neurological deficit lasting >24 h with computed tomography or magnetic resonance imaging evidence of cerebral ischemic infarct or intracerebral hemorrhage.

Secondary outcomes, all at 1 year post-procedure, included death, MI, stroke, subsequent ipsilateral lower extremity bypass grafting, and ipsilateral major amputation, defined as any amputation above the level of the ankle joint. To account for the competing hazard of death among patients at high risk of needing amputation, we also evaluated amputation-free survival as a composite endpoint.

Lesion-specific secondary outcomes included primary, primary assisted, and secondary patency of all lesions treated with endovascular intervention. Loss of primary patency was defined as a velocity ratio of ≥2.0 as assessed by duplex ultrasonography or endovascular or surgical reintervention to the target vessel. Primary assisted patency was defined as patency after treatment for restenosis, and secondary patency was defined as overall patency after restenosis or occlusion.

All outcomes were adjudicated from physician documentation in the electronic medical record. To ensure that deaths outside our institution were captured, patient vital status was also verified using the Social Security Death Index.

Data analysis. Values of mean ± SD were used to describe continuous variables, and frequencies and percentages were used for categorical variables. Continuous variables were compared using the Wilcoxon rank sum test or analysis of variance, and categorical values using the chi square or Fisher exact test. All analyses were performed using Stata version 11.2 (StataCorp LP, College Station, Texas).

We developed propensity scores to adjust for confounding in statin use, defined as the conditional probability of being treated with a statin given a patient's measured demographic and clinical characteristics (15). To calculate the propensity score for statin treatment, we developed a logistic model for statin treatment using stepwise logistic regression analysis. Baseline covariates in the model included age, sex, and race; history of diabetes, coronary artery disease (CAD), MI, hypertension, heart failure, stroke, carotid artery disease, or chronic obstructive pulmonary disease; smoking status; left ventricular ejection fraction (in 5% increments from ≤10% to ≥65%); prescription of concomitant medications including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, aspirin, and clopidogrel; and year of procedure.